Lay Abstract

While therapy has improved the survival rates for many cancers, both adult and childhood sarcomas and neuroblastoma remain a formidable challenge in oncology. The survival of patients with relapsed, refractory, or metastatic disease remains dismal, and has not significantly improved with modern therapy. There is no doubt that new types of therapies must be developed for these patients.

The idea of injecting tumors with infectious agents, which normally kill an infected cell, to elicit tumor shrinkage dates back at least a century. Only in recent years, however, new understandings of the inner workings of cancer cells, combined with knowledge of how viruses interact with cells and how to manipulate virus genes, come together to allow us to rationally test viruses as a new approach to cancer therapy.

So-called "oncolytic" viruses are appealing as treatment for cancer because they have multiple anticancer mechanisms. Oncolytic viruses cause direct tumor cell death independent of cells that are not killed by chemotherapy or radiotherapy. These viruses can spread by themselves throughout a tumor and shrink bulky disease. Viruses can also be used to deliver therapeutic genes, further expanding the potential anti-tumor mechanisms utilized by a single agent. Virus infection can also help activate a person's immune system to fight the cancer.

The mutated virus we propose to use, called HSV1716, is a defective version of the Herpes simplex type 1 virus (HSV1). HSV1 is spread by contact with saliva and is commonly acquired during childhood. By the age of 15 years, –75% of people have been exposed to HSV. Exposure reaches its peak of 85% of people by age 40 years. The virus typically causes mouth sores and becomes latent (dormant) in the neurons of the spinal cord. Various types of stress cause the virus to re-emerge from the neuron, resulting in a recurrent mouth or lip sore ("cold sore"). On rare occasions the virus can also cause infection of other organs such as liver (hepatitis), eye (keratitis), throat (esophagitis), and brain (encephalitis). Fortunately, medications are available to treat HSV1 infection including acyclovir, valacyclovir, ganciclovir, and famciclovir, which can be given by topical, oral, or intravenous routes.

The virus HSV1716 is a crippled version of HSV1 due to the deletion of the gene encoding the protein ICP34.5. HSV1716 does not divide or spread when it gets into most cells in the body. Most cancer cells divide rapidly in the body and so permit the replication of HSV1716. Thus, HSV1716 replicates and spreads quite well in most cancer cells even under normal conditions.

HSV1716 has been shown to be safe to give to humans. It has been injected directly into the tumors of the brain, soft tissues (head and neck cancer carcinoma), and skin (melanoma). Because we have shown in cultured cells and in mouse models that defective HSV 1 viruses are toxic for sarcomas and neuroblastomas that are found in children and young adults, testing the safety of HSV I mutants in these patients who have no other treatment options is a next logical step. The inclusion of children is essential in

order for this type of therapy to be tested on deadly diseases that are unique to pediatric oncology.

In our study, we will enroll patients who have exhausted all known effective treatment options and who will die of their disease. Tumors will be directly injected with virus through a needle placed under ultrasound or computed tomography (CT) guidance by an interventional radiologist. In cases where a surgical debulking of the tumor is deemed safe, virus will be directly injected into the tumor bed. If patients do not experience excessive toxicities, repeat injections will be performed every 3 weeks up to four times. During those subsequent procedures, core needle biopsies of tissue will also be obtained to assess virus replication in the tumor. Blood and urine samples will also be screened periodically for virus. Anyone experiencing clinical symptoms consistent with encephalitis or hepatitis will be treated with one of the antiviral drugs, and the trial will be stopped. Three patients (age 13-30) will be enrolled at each of two dose levels.

This study will help us determine whether this type of virus administration is safe in these patients, and may give hints of whether there is any anti-tumor effect. Successful completion of the trial will open up the possibility of further testing of this potential new treatment for these and other deadly cancers.